

## Assessment of Nephroprotective Potentials of *Citrus aurantifolia* (Christm) Swingle Peels Extract in Gentamicin-Induced Kidney Toxicity in Mice

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

### Abstract

**Background:** Peels from *Citrus aurantifolia* are used in ethnomedicine to cure a variety of illnesses. These extracts have been used traditionally as cold treatments, anti-inflammatory, and antibacterial agents, suggesting that they could be used in contemporary nephroprotective drugs.

**Objective:** The objective of this investigation was to assess the nephroprotective properties of *Citrus aurantifolia* peels extract (CAPE) in gentamicin-induced kidney toxicity.

**Method:** Dried *Citrus aurantifolia* peels were extracted with 80% methanol. Thirty mice were randomly assigned to six groups (Groups 1-6, n = 5). Group I received normal saline only (10 mL/kg; baseline), while Groups II, III, IV, V, and VI received gentamicin (100 mg/kg) intraperitoneally to induce kidney toxicity, with concomitant administration of normal saline (10 mL/kg), different doses of CAPE (100, 200, and 400 mg/kg), and ascorbic acid (200 mg/kg), respectively. Treatments were administered orally for 8 days. Twenty-four hours after the final dose, blood samples were collected, allowed to clot, and centrifuged to separate the serum for measuring urea, creatinine, and blood urea nitrogen (BUN). Furthermore, the levels of malondialdehyde (MDA) and glutathione (GSH) in kidney tissue were assessed.

**Results:** The data indicated a decrease in tissue MDA, serum creatinine, urea, and BUN in the CAPE-treated groups. Moreover, the CAPE-treated groups exhibited elevated tissue CAT activity and higher GSH concentrations.

**Conclusion:** The study concluded that CAPE displayed nephroprotective effects, which were possibly mediated via inhibition of oxidative stress.

**Keywords:** methanol, *Citrus aurantifolia*, Nephroprotective, Gentamicin, Antioxidants

### INTRODUCTION

When it comes to nephrotoxic medications like gentamicin, the kidney is the organ most susceptible. A quick decline in kidney function brought on by a number of causes is known as nephrotoxicity. The

nephrotoxicity caused by gentamicin (GM) was demonstrated by a rise in serum renal biomarkers (Kedir *et al.*, 2022). One of the most frequent forms of renal impairment is drug-induced kidney injury, of

which gentamicin accounts for about 25% (Akinaw *et al.*, 2024). Gentamicin is an aminoglycoside antibiotic that can be used to cure a variety of infections quickly due to its bactericidal properties. However, using it for longer than seven days at high dosages can have nephrotoxic adverse effects (Dik *et al.*, 2024). Because gentamicin can cause kidney damage through oxidative stress and inflammation, its nephrotoxicity in mice is a serious concern (Akinaw *et al.*, 2024).

Since many medications and chemicals can cause nephrotoxicity due to oxidative stress, it stands to reason that substances with antioxidant properties can shield the kidney from oxidative damage and enhance renal function (Hilmi *et al.*, 2023). Antioxidants and herbal extracts have been highlighted as preventive agents against this nephrotoxic impact in a number of studies (Akinaw *et al.*, 2024).

*Citrus aurantifolia* fruits are farmed worldwide in tropical and subtropical locations, with an approximate annual production of 102 million tons. They are members of the Rutaceae family. In addition to significant amounts of several other elements such as minerals, vitamins, micronutrients, and dietary fibers, they are high in vitamin C. According to Saleem *et al.* (2023), these ingredients are thought to be a crucial

component of the human diet. Citrus fruits may be able to help prevent oxidative damage to cells because they are a great source of antioxidants such as phenolic compounds, ascorbic acid, essential oils, and carotenoids (Vlaicu, *et al.*, 2020).

One of the main sources of phenols and flavonoids is the peel from different citrus species (Chung, 2018). Because phenolic compounds have antibacterial, anti-inflammatory, anticancer, and cardioprotective properties, they also exhibit great promise as therapeutic agents. Numerous health benefits of antioxidant chemicals make them attractive candidates for use in medical applications (Cory *et al.*, 2021). Many ailments, including stomachaches, cancer, diuretics, colds, immune system disorders, bacterial and viral infections, digestive system disorders, and vitamin deficiencies, are traditionally treated with *Citrus aurantifolia* peels using folklore and traditional medicine (Yerou *et al.*, 2017; Liu *et al.*, 2021). The purpose of this study was to examine the nephroprotective potentials of *Citrus aurantifolia* (Christm) swingle peels extract in gentamicin-induced kidney damage using mice, taking into account the previously described ethnopharmacology features of the plant.

## Methodology

### Chemicals

We obtained glutathione, hydrogen peroxide, epinephrine, and 5,5-dithios-bis-2-nitrobenzoic acid from Sigma Chemical Co. in Saint Louis, Missouri, in the United States. Thiobarbituric acid, trichloroacetic acid, and absolute ethanol from British Drug House Chemical Ltd. in Poole, UK were used. Every chemical used was of analytical grade.

### Plant Collection and Identification

*Citrus aurantifolia* (Christm.) Swingle fruits were obtained from Ibadan, located in Oyo State, southwest Nigeria. At the Department of Botany Herbarium, University of Ibadan, Oyo State, Nigeria, the plant was recognized by taxonomist D.P.O. Esimekhuai. The same herbarium contains a voucher specimen (UIH-22957).

### Extraction of plants

The 200 g peels were crushed and extracted over the course of 72 hours using a solution of 80% methanol (1.0 L) and 20% water (0.2 L), filtered and concentrated using a water bath at 60°C. The crude

methanol extract was stored at -20°C prior to the studies.

### Phytochemical analysis of crude extract

Using the procedures described by Trease and Evans (2002), a qualitative phytochemical screening of the *Citrus aurantifolia* peels extract (CAPE) was performed.

### Study design

Thirty mice each weighing between 18-22 g were randomly distributed into six groups of five mice per group as follows:

Group 1: Normal control (mice received standard diet and 0.2 mls Normal saline orally for 8 days)

Group 2: 100 mg/kg GM, I.P. + 0.2 mls Normal saline (N/S) orally for 8 days

Group 3: 100 mg/kg GM, I.P. + 0.2 mls CAPE 100 mg/kg orally for 8 days

Group 4: 100 mg/kg GM, I.P. + 0.2 mls CAPE 200 mg/kg orally for 8 days

Group 5: 100 mg/kg GM, I.P. + 0.2 mls CAPE 400 mg/kg orally for 8 days

Group 6: 100 mg/kg GM, I.P. + 0.2 mls 200 mg/kg Ascorbic acid orally for 8 days

### Preparation of samples

Using a heart puncture, blood samples were taken into plain centrifuge tubes at the end of the experiment. The serum was separated by centrifuging the tubes after they had sat for two hours. Creatinine, urea, and blood urea nitrogen levels were measured in the serum. After dissection, the kidneys were removed, rinsed in ice-cold 1.15% KCl wiped dry, and weighed. Using a Potter-Elvehjem homogenizer, kidney samples were then homogenized in four volumes of 50 mM phosphate buffer (pH 7.4). The post-mitochondrial supernatant fraction (PMF), which was used to

## RESULTS

### Phytochemical screening

The preliminary qualitative and quantitative screening of methanol extract of *Citrus aurantifolia* peels was

### Effect of *Citrus aurantifolia* peel extract in Gentamicin-induced kidney toxicity on Kidney function test

#### Serum Creatinine level

CAPE significantly ( $p < 0.05$ ) reduced creatinine levels compared to the control (GM+N/S) in a dose dependent manner. CAPE (200 and 400 mg/kg) exhibited a significant ( $p < 0.05$ ) reduction in creatinine levels relative to GM+N/Saline (Table 1).

#### Urea level

A significant ( $p < 0.05$ ) increase in serum urea levels was observed in GM+N/S group relative to Normal

measure the levels of glutathione (GSH) and malondialdehyde (MDA), was then obtained by centrifuging the samples at 10,000 g for 15 minutes

### Biochemical parameters determination

Utilizing techniques described by Oyinloye et al. (2020), were used to determine serum levels of and the amounts of glutathione and malondialdehyde in kidney tissues.

### Statistical analysis

Data obtained were analysed using the Graph Pad Prism statistical package version 6.01. Values were expressed as mean  $\pm$  SEM. Differences in mean between more than two groups were compared using one-way ANOVA and Newman-Keuls post hoc test was employed for multiple comparisons of treatment groups. Level of statistical significance was determined at  $p < 0.05$

carried out. The following phytoconstituents viz., Alkaloids, Terpenoids, Tanins, Phenol, Flavonoids and Saponins were identified in the sample.

saline administered group. The results showed decrease in urea levels by CAPE (100, 200 and 400 mg/kg) in a dose dependent fashion compared to the GM+N/S. The effect of CAPE (400 mg/kg) on urea was comparable to the standard (Ascorbic acid) (Table 1).

#### Blood Urea Nitrogen level

The group administered with GM + Normal saline exhibited a substantial ( $p < 0.05$ ) increase in serum blood urea nitrogen level in comparison with group treated with Normal saline. On the contrary, CAPE (400 mg/kg) and GM + Ascorbic acid produced a comparable decrease in uric acid levels against the GM + Normal saline (Table 1).

**Table 1: Effect of *Citrus aurantifolia* peels extract in Gentamicin induced kidney toxicity on Kidney function test**

S/N	TREATMENT GROUPS	CREATININE (mg/dl)	UREA (mg/dl)	BLOOD UREA NITROGEN (BUN) (mg/dl)
1	Normal/Saline (N/S)	1.16±1.3	8.44±0.7	5.41±0.3
2	GM + Normal/Saline	5.17±0.1 <sup>#</sup>	25.84±1.3 <sup>#</sup>	11.14±1.2 <sup>#</sup>
3	GM + CAPE 100 mg/kg	3.10±1.5	23.5±1.1	11.00±0.4
4	GM + CAPE 200 mg/kg	2.62±0.1*	21.23±0.2	9.38±0.6
5	GM + CAPE 400 mg/kg	2.41±1.8*	18.48±1.0	7.94±1.4
6	GM + Ascorbic/acid 200 mg/kg	2.02±1.2*	18.21±2.1	7.15±1.5

GM-Gentamicin, N/S-Normal/Saline, CAPE- *Citrus aurantifolia* peel extract. <sup>#</sup>=  $p < 0.05$  significant against Normal saline; \* =  $p < 0.05$  significant against GM + Normal saline

### Effect of *Citrus aurantifolia* peels extract in Gentamicin induced kidney toxicity on antioxidant markers

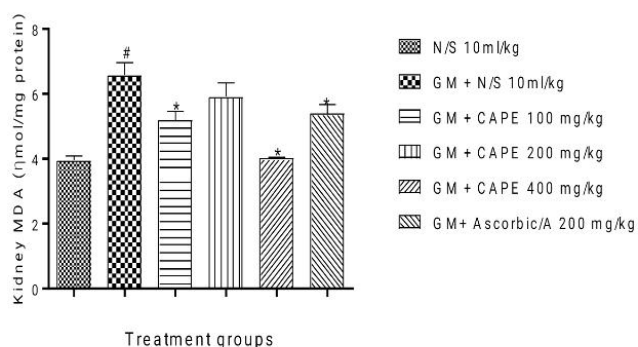
#### Malondialdehyde (MDA)

Figure 1. Demonstrated a significant ( $p < 0.05$ ) elevation in the MDA level in the kidney tissue homogenate of GM + N/saline compared with control group (N/saline). In contrast, CAPE (100, and 400 mg/kg) significantly decreased the MDA level ( $p < 0.05$ ) relative to GM + N/saline. In addition, GM + CAPE 400 mg/kg produced a better significant

reduction in MDA level ( $p < 0.05$ ) against the GM + N/saline than GM + Ascorbic acid.

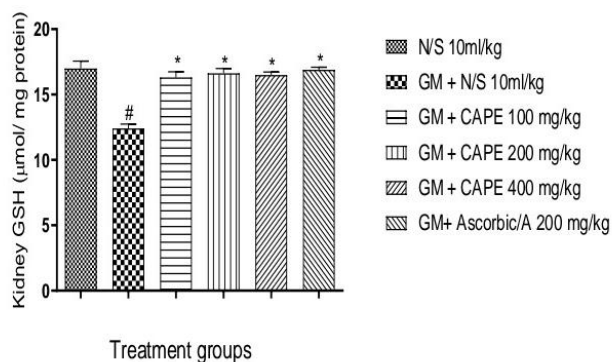
#### Glutathione (GSH)

A significant ( $p < 0.05$ ) decreased in GSH levels was observed in group administered with GM + N/saline when compared with control (N/saline). Furthermore, there were significant ( $p < 0.05$ ) increases in GSH levels in groups administered with CAPE 100, 200 and 400 mg/kg relative to GM + N/saline, comparable to positive control GM + Ascorbic acid (Figure 2).



GM-Gentamicin, N/S-Normal/Saline, CAPE- *Citrus aurantifolia* peels extract, MDA- Malondialdehyde, Ascorbic/A-Ascorbic acid. <sup>#</sup>=  $p < 0.05$  significant against Normal saline; \* =  $p < 0.05$  significant against GM + Normal saline (One way ANOVA followed by Newman-Keuls post hoc test). Values represent the mean  $\pm$  S.E.M. for 5 animals per group.

**Figure 1: Effect of CAPE on kidney malondialdehyde (MDA) level in Gentamicin-induced mice.**



GM-Gentamicin, N/S-Normal/Saline, CAPE- *Citrus aurantifolia* peels extract, GSH- reduced glutathione (GSH) Ascorbic/A-Ascorbic acid. #=  $p < 0.05$  significant against Normal saline; \*=  $p < 0.05$  significant against GM + Normal saline (One way ANOVA followed by Newman-Keuls post hoc test). Values represent the mean  $\pm$  S.E.M. for 5 animals per group.

**Figure 2: Effect of CAPE on kidney reduced glutathione (GSH) level in Gentamicin-induced mice**

## DISCUSSION

Even at therapeutic levels, gentamicin-induced kidney damage is one of the most concerning adverse effects of aminoglycoside antibiotics, which are used to treat serious infections against Gram-negative bacteria (Zeeni *et al.*, 2007). Functionally, gentamicin-induced renal toxicity is defined by elevated serum creatinine, urea, and uric acid levels, as well as renal dysfunction. Structurally, it is linked to glomerular atrophy, tubular necrosis and fibrosis, perivascular edema, inflammation, and glomerular congestion (Soliman *et al.*, 2007; Al-Shabanah *et al.*, 2010). As a result of oxidative stress, gentamicin has been shown to cause severe nephrotoxicity.

Gentamicin often builds up in the renal proximal tubules and causes the mitochondria to produce hydrogen peroxide, which speeds up the process of oxidative stress (Ueda *et al.*, 1993). One of the most common methods for lowering nephrotoxicity caused by gentamicin is to employ recognized antioxidants, such as vitamin C and E (Ajith *et al.*, 2007). In order to reduce the harmful effects of gentamicin on the kidney, efforts have been directed in recent years toward the creation of antioxidants from natural sources, such as fruits, vegetables, and herbs (Ali, 2003; Badary *et al.*, 2005).

Numerous studies have shown that *Citrus aurantifolia*, or lime, has nephroprotective qualities against drug-induced kidney damage. Because of its anti-inflammatory and antioxidant properties, which lessen oxidative stress and cellular damage, it is thought to have protective effects. Strong antioxidant activity in flavonoids and other secondary metabolites found in

Citrus can prevent oxidative stress brought on by gentamicin (Nasution *et al.*, 2020). The larger potential of citrus fruits in renal health is highlighted by the nephroprotective benefits of other citrus extracts, such as *Citrus sinensis* and *Citrus medica*, against gentamicin toxicity (Al-Yahya *et al.*, 2015).

This study shows that gentamicin causes renal damage in mice by increasing blood urea nitrogen (BUN), creatinine, and urea levels as well as by increasing malondialdehyde (MDA) concentrations and decreasing reduced glutathione (GSH) contents in kidney tissue. According to earlier research, these alterations demonstrate that gentamicin caused renal impairment (El-Tantawy *et al.*, 2013). The index of nephrotoxicity is defined as elevated levels of creatinine, urea, and BUN (Al-Yahya *et al.*, 2015). The most significant indicators for evaluating renal damage in laboratory animals are believed to be mostly urea and BUN estimation (Guyton, 1991). Since serum creatinine and urea are the main final purine metabolites, changes in the glomerular filtration rate may increase the levels of these metabolites in the serum and linked to damage to the kidneys (Al-Yahya *et al.*, 2015).

Renal function biomarkers in the current study demonstrated that co-treatment of *Citrus aurantifolia* peels extract (CAPE) for eight days effectively prevented renal damage associated with gentamicin. This study was in line with earlier findings by Oyinloye *et al.* (2024), who investigated attenuating potentials of *Citrus aurantifolia* (Chrism.) Swingle peels extract in doxorubicin-induced nephrotoxicity. The kidney is more susceptible to harmful interactions

even though GSH is only found in trace amounts there (Sohn *et al.*, 2009). The significant increase in GSH levels in the renal tissue shown in the group treated with gentamicin was due to the effect of CAPE.

Previous investigations had shown that, antioxidants ameliorate gentamicin-related nephropathy. (Begum *et al.*, 2006; Pedraza-Chaverri *et al.*, 2000). Moreover, oxidative effects of gentamicin have been linked to renal cortex injury in earlier studies (Yaman and Balıkcı, 2010). The current study's enhanced MDA content, a lipid peroxidation marker, demonstrated gentamicin-induced lipid peroxidation. Our findings demonstrated a diminishing lipid peroxidation process in kidney tissue, as seen by the considerable reduction in kidney MDA levels in groups treated with gentamicin plus graded doses of CAPE (100, 200 and 400 mg/kg). *Citrus aurantifolia* peels extract (400

mg/kg) in this study prevented renal injury and restored the kidneys' antioxidant status.

The results of this investigation showed that the administration of CAPE reduced the nephrotoxic effects of gentamicin by lower blood urea nitrogen, urea, renal tissue MDA levels, and serum creatinine concentration. Our phytochemical screening results are consistent with published reports by Oyinloye *et al.* (2020) and Oyinloye *et al.* (2024) on *Citrus aurantifolia* peels extract, which demonstrated the presence of flavonoids, alkaloids, phenol, tannins, and saponins. *Citrus aurantifolia* peels extract has been found to have noteworthy antioxidant and free radical scavenging properties, along with a significant concentration of phenolic compounds and d-limonene (Oyinloye *et al.*, 2024).

## CONCLUSION

This research offers an understanding of the pharmacological applications of fruit peels extract as a possible antioxidant and nephroprotective agent. Some really encouraging effects are shown by the *Citrus aurantifolia* peels extract, due to the presence of significant amounts of beneficial phytochemicals including flavonoids and phenolic compounds, the fruit peels under investigation can be a rich source of

natural antioxidants. Additionally, the examined extracts showed significant scavenging activity. The results obtained from this investigation could be useful in identifying new avenues for future research concerning the use and implementation of the examined extracts as pharmacological and nutraceutical interventions.

## REFERENCES

- Ajith, T.A., Usha, S and Nivitha, V. (2007). Ascorbic acid and alpha-tocopherol protect anticancer drug cisplatin induced in mice: a comparative study. *Clin Chim Acta* 375(1-2): 82-6.doi: 10.1016/j.cca.2006.06.011.
- Akinaw, M., Nair, S.P., Usure, R., Leta, B., Kedir, A., Mamo, S.A., Waritu, N., Jemal, M and Mulat, B. (2024). Nephroprotective Effect of the Leaf Extract of *Ajuga remota* Benth Against Gentamicin-Induced Nephrotoxicity in Swiss Albino Mice. *J. Exp. Pharmacol.* 16:159-171
- Ali, B.H. (2003). Agents ameliorating or augmenting experimental gentamicin nephrotoxicity:some recent research. *Food Chem. Toxicol.* 41(11):1447-52
- Al-Shabanah, O.A., Aleisa, A. M., Al-Yahya, A.A., Al-Rejaie, S.S., Bakheet, S.A and Fatani, A.G. (2010). Increased urinary losses of carnitine and decreased intramitochondrial coenzyme A in gentamicin-induced acute renal failure in rats. *Nephrol. Dial. Transplant.* 25(1):69.
- Badary, O.A., Abdel-Maksoud, S., Ahmed, W.A and Owieda, G.H. (2005). Naringenin attenuates cisplatin nephrotoxicity in rats. *Life Sci.* 76(18):2125-35. Doi: 10.1016/j.ifs.2004.11.005.
- Balakumar, P., Rohilla, A and Thangathirupathi, A. (2010). Gentamicin-induced nephrotoxicity: Do we have a promising therapeutic approach to bunt it. *Pharmacol Res* 62(3): 179.
- Begum, N.A., Dewan, Z.F., Nahar, N and Mamun, M.I. (2006). Effect of n-hexane extract of *Nigella sativa* on gentamicin-induced nephrotoxicity in rats. *Bang. J. Pharmacol.* 1(1):16
- Chung, D., Cho, T.J and Rhee, M.S. (2018). Citrus fruit extracts with carvacrol and thymol eliminated 7-log acid-adapted *Escherichia coli* O157: H7, *Salmonella typhimurium*, and *Listeria monocytogenes*: a potential of effective natural antibacterial agents. *Food Res. Int.* 107:578–588.
- Cory, H., Passarelli, S., Szeto, J., Tamez, M and Mattei, J. (2018). The role of polyphenols in human health and food systems: a mini-review. *Front. Nutr.* 5:87. doi:10.3389/fnut.2018.00087.
- Czech, A., Malik, A., Sosnowska, B and Domaradzki, P. (2021). Bioactive substances, heavy metals, and antioxidant activity in whole fruit, peel, and pulp of citrus fruits. *Int. J. Food Sci.* 2021(1):6662259. <https://doi.org/10.1155/2021/6662259>.
- Dik, B., Hatipoğlu, D and Ateş, M.B. (2024). Potential effects of Resatorvid and alpha lipoic acid on gentamicin-induced nephrotoxicity in rats. *Pharmacol. Res. Perspect.* 12(4): e1222. Doi:10.1002/prp2.1222.

- El-Tantawy, W. H., Mohamed, S.A and Abd Al Haleem, E. N. (2013). Evaluation of biochemical effects of *Causuarina equisetifolia* extract on gentamicin-induced nephrotoxicity and oxidative stress in rats. Phytochemical analysis. *J. Clin. Biochem. Nutr.* 53(3):158-165. Doi: 10.3164/jcbrn.13-19.
- Guyton, A. C. (1991). 8th ed. Philadelphia: WB Saunders Company. 344.
- Hilmi, S., Dewan, Z.F., Kabir, A.N., Islam, M.M., Yusuf, M.A., Afreen, K.N and Akter, M. (2023). Effect of Silymarin on Gentamicin Induced Nephrotoxicity in Rats. *Bangladesh journal of infect. dis.* 10(2):71-76
- Kedir, W.M., Dubiwak, A.D and Ahmed, E.F. (2022). Nephroprotective Effect of Asparagus africanus Lam. Root Extract against Gentamicin-Induced Nephrotoxicity in Swiss Albino Mice. *J. Toxicol.* 2022:1-8.
- Liu, N. et al. (2021). A review of chemical constituents and health-promoting effects of citrus peels, *Food Chem.* 365:130585.
- Nasution, M., Ginting, C.N., Fachrial, E and Lister, I.N.E. (2020). Potency of Sunkit Orange (*Citrus sinensis*L. Osbeck) against Kidney Histology of White Wistar Rats Induced by Gentamicin. *Trad. Med. J.* 25(1):42-48. <https://doi.org/10.22146/mot.49107>.
- Oyinloye, E.O., Murtala, A.A., Olooto, W.E., Ajayi, A.M and Omogbai, E.K.I. (2020). Evaluation of membrane stabilizing, anti-inflammatory, antihyperalgesia effects of *citrus aurantifolia* (christm) swingle peel extract in rats. *Journ. Pharm. Sci.*19(1):01-09.
- Oyinloye, E.O., Murtala, A.A., Oladoja, F.A., Aderinola, A.A., Okunye, L.O., Saka, S.A., Abolarinwa, J.A., Kasumu, O.E and Osipitan, L.E. (2024). *Citrus aurantifolia* (Chrism.) Swingle peel extract attenuate nephrotoxicity induced by doxorubicin. *Pharmacol. Res. –Mod. Chin. Med.* 11:100412. <https://doi.org/10.1016/j.prmcm.2024.100412>.
- Pedraza-Chaverri, J., Maldonado, P. D., Medina-Champos, N., Olivares-Corichi, I. M., Granados-Silvestre, M. L and Hernandez-Pando, R. (2000). *Free Rad. Biol. Med.* 29(7): 602.
- Saleem, M., Durani, A.I., Asari, A., Ahmed, M., Ahmad, M., Yousaf, N and Muddassar, M. (2023). Investigation of antioxidant and antibacterial effects of citrus fruits peels extracts using different extracting agents: Phytochemical analysis with in silico studies. *Heliyon.* 9: e15433.
- Sohn, S. H., Lee, E. Y., Lee, J. H., Kim, Y., Shin, M and Hong, M.et al. (2009). Screening of herbal medicines for recovery of acetaminophen-induced nephrotoxicity. *Environ. Toxicol. Pharmacol.* 27(2), 225.
- Soliman, K. M., Abdul-Hamid, M and Othman, A. I. (2007). Effect of Carnosine on gentamicin-induced nephrotoxicity. *Med Sci Monit* 13(3):73-83.
- Ueda, N., Guidet, B and Shah, S. V. (1993). Gentamicin-induced mobilization of iron from renal cortical mitochondria. *Am J Physiol* 265(3): F435-9.
- Vlaicu, P.A.I., Panaite, T. D., Untea, A.E., Saracila, M and Margareta, O (2020). Nutritional characterization and the antioxidant properties of sweet orange and red grapefruit peels. *Lucrări Științifice-Universitatea de Științe Agricole și Medicină Veterinară, Seria Zootehnie.* 73:112–118.
- Yaman, I and Balıkcı, E. (2010). Protective effects of nigella sativa against gentamicin-induced nephrotoxicity in rats. *Exp Toxicol Pathol.* 62(2),183-90. Doi: 10.1016/j.etp.2009.03.006. Ephub 2009
- Yerou, K.O., Ibri, K., Djilali, B., Ahmed, H., Medda, B and Aicha, T.T.M.. (2017). The use of orange (*citrus sinensis*) peel as antimicrobial and anti-oxidant agents. *J. Fund. Appl. Sci.* 9 (3): 1351–1357.
- Zeeni, N., Selmaoui, B., Beauchamp, D., Labrecque, G and Thibault, L. (2007). Dietary protein level alters gentamicin-induced nephrotoxicity. *Physiol Behav.* 90(5), 760-770. <https://doi.org/10.1016/j.physbeh.2006.12.018>.

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